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REPORT

Immunopathology of psoriasis and psoriatic arthritis

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Psoriatic arthritis (PsA) is characterised by several unique clinical features that differentiate it from rheumatoid arthritis (RA). Attempts to identify immunopathological mechanisms, some shared with psoriasis, that underlie these differences from RA have been most challenging. Recent research studies, however, highlight novel findings in PsA at the molecular, cellular, and tissue levels that form the basis for a new understanding of this relatively common form of inflammatory arthritis. In particular, the availability of new, biological antitumour necrosis factor α therapies have allowed further insight into the immunopathology of psoriasis and PsA. This brief review focuses on immunohistological studies in psoriatic skin, PsA synovium, and bone to demonstrate how these data advance our knowledge of disease pathogenesis.

The nature of the inflammatory infiltrate in the skin and joints has been the subject of detailed investigation. In both tissues there is a prominent lymphocytic infiltrate, localised to the dermal papillae in skin and to the sublining layer stroma in the joint.^{1, 2} Recent evidence suggests a similar infiltrate is found at the inflammatory entheses.³

CELLULAR IMMUNOPATHOLOGY

The cellular infiltrate is predominantly in a perivascular distribution, although cells may migrate to the lining layer of the joint or the epidermis. In addition, abundant B lymphocytes may form primitive germinal centres; the function of these B cells is not clear, as psoriasis and psoriatic arthritis (PsA) are not associated with high circulating antibody levels.^{1, 3} T lymphocytes are the most common inflammatory cells in the skin and joints.^{1, 2} CD4+ T cells are the most significant lymphocytes in the tissues, with a CD4+/CD8+ ratio of 2:1; in contrast, this ratio is reversed in the synovial fluid compartment and at the entheses, where CD8+ T cells are more common.^{3, 4}

There is evidence that CD8+ T cells populate the developing skin lesion first, and lymphocyte specific therapy results in a reduction of CD8+ T cells in the epidermis, which correlates with clinical improvement.^{5, 6} A dominant CD8+ T cell population in PsA synovial fluid suggests that these cells may be driving the immune response in the joint.⁷ This is supported by an association of PsA with human leucocyte antigen (HLA) class I,⁸ with human immunodeficiency virus (HIV) infection, and selective CD4 depletion.⁹ T cell receptor (TCR) repertoire oligoclonality more commonly expressed in the CD8+ T cell population has been identified in epidermal cells¹⁰ and the skin, and in the synovium¹¹ and the synovial fluid compartment⁷ of patients with PsA. More recently, we have extended these studies to synovial tissue. Curran *et al* analysed and compared the TCR repertoire in synovium obtained from joints during active inflammation and the same tissue following methotrexate induced remission.¹² The main effect of methotrexate was to greatly diminish

the dominant inflammation related, unexpanded, and minimally expanded CD4 and CD8 lineage populations, none of which persisted after methotrexate treatment. In contrast, only the minor population of putatively antigen driven CD8 T cell clones that have a highly expanded precursor pool in blood persist despite methotrexate therapy. These observations support the concept of a "three cell interaction" with effector CD8+ cells and regulatory CD4+ T cells both interacting with antigen presenting cells (APCs), such as the Langerhans cell.¹³ In addition to APCs, natural killer receptor expressing cells (NKR) may be involved; a pathophysiological role for the interaction between NKR-T cells and CD1d on keratinocytes has been suggested in a severe combined immunodeficiency (SCID) mouse model engrafted with "non-lesional" psoriasis.¹⁴

T cells access the joint by first binding to activated endothelial cells via cell adhesion molecules (CAM) expressed on their surface. Upregulation of intercellular adhesion molecule-1 (ICAM-1) and vascular adhesion molecule-1 (VCAM-1) is pronounced in the skin and synovial membrane; however E-selectin appears to be upregulated in the skin more than in the PsA synovial membrane.^{1, 15} In addition, cutaneous lymphocyte associated antigen (CLA) is preferentially expressed on leucocytes "homing" to lesional psoriatic skin but not to the PsA synovial membrane.¹⁶ Recent evidence suggests that local expression of myeloid related protein also plays a central role in transendothelial migration of leucocytes in PsA.¹⁷

VASCULAR IMMUNOLOGY

Specific vascular morphological changes have been described in the psoriasis skin,^{18, 19} nailfold capillaries,^{20, 21} and, more recently, in PsA synovial membrane, suggesting a common link.²² Angiogenesis is a prominent early event in psoriasis and PsA,^{23, 24} elongated and tortuous vessels in skin and joint suggest dysregulated angiogenesis resulting in immature vessels. Angiogenic growth factors including transforming growth factor β (TGF β), platelet derived growth factor (PDGF), and vascular endothelial growth factor (VEGF) are markedly increased in psoriasis.²⁵ VEGF and TGF β levels are high in the joint fluid in early PsA,²⁶ and expression of angiopoietins, a novel family of vascular growth factors, colocalise with VEGF protein and mRNA in PsA synovial membrane perivascular areas. Angiopoietin expression is upregulated in perivascular regions in lesional psoriasis skin.^{27, 28}

The common features of vascular morphology and angiogenic growth factors in the skin and joints, in addition to

Abbreviations: APC, antigen presenting cell; CLA, cutaneous lymphocyte associated antigen; HLA, human leucocyte antigen; ICAM, intercellular adhesion molecule; IL, interleukin; MHC, major histocompatibility complex; MMP, matrix metalloproteinase; NKR, natural killer receptor (cell); PsA, psoriatic arthritis; RA, rheumatoid arthritis; RANK(L), receptor activator of nuclear factor κ B (ligand); TCR, T cell receptor; TGF, transforming growth factor; TNF, tumour necrosis factor; VEGF, vascular endothelial growth factor; VCAM, vascular cell adhesion molecule

similarities in expression of neuropeptides, may reflect a common neurovascular pathway. Koebner's phenomenon is the development of psoriasis on areas of skin irritated by mechanical, physical, or chemical agents. Koebner's reaction may result from release of potent proinflammatory neuropeptides from nerve endings.²⁹ The nervous system has been implicated by the observation in a case report that substance P release from the synovial membrane into joint fluid is blocked by nerve damage.³⁰ In another case report, digital denervation prevented the development of arthritis in the digital interphalangeal joints.³¹ These observations support a hypothesis of direct neural activation in the translation of a stress/traumatic stimulus into an immunological response.³²

CYTOKINES, METALLOPROTEINASES, AND CARTILAGE DEGRADATION

In a recent study, we examined the relations between local and systemic markers of inflammation, the levels of cytokines and matrix metalloproteinases (MMPs) in synovial fluid, and markers of cartilage metabolism in early arthritis.³³ We demonstrated high levels of tumour necrosis factor α (TNF α), interleukin (IL)-10, and MMPs in the joint fluid of patients with early PsA, confirming a previous study which found increased production of these cytokines in cell cultures from PsA joints.³⁴ In addition, Fraser *et al* demonstrated a direct correlation between the levels of TNF α , MMP-1, and markers of collagen degradation—further evidence that collagenase cleavage of cartilage collagen begins early in the disease and probably results from cytokine driven production of proteases.³³

ROLE OF TNF α IN PSORIASIS AND PSORIATIC ARTHRITIS

TNF α is a key proinflammatory cytokine capable of driving inflammation in a number of different clinical settings. That TNF α plays an important role in psoriasis and PsA has been demonstrated in a number of ways. Firstly, the TNF α protein and message in skin and synovial tissue has been well documented. Secondly, TNF α gene polymorphism analysis also suggests a role for TNF α if not in disease initiation quite likely in disease severity. Thirdly, evidence from clinical trials strongly supports a role for TNF α inhibition, as a high degree of clinical benefit in both skin and joint disease has been demonstrated.

TNF α in psoriasis

As outlined above, there is considerable evidence that psoriasis and PsA are T cell driven diseases. T cells may achieve this by direct effects or indirectly through the release of various chemokines and cytokines, including TNF α , that signal the keratinocytes to hyperproliferate.³⁵ These signalling molecules are believed to play a key role in amplifying the inflammatory process.³⁶ Increased concentrations of TNF α have been detected in psoriatic skin lesions, and TNF α has been shown to upregulate endothelial and keratinocyte expression of ICAM-1, which plays an important role in cellular adhesion and trafficking. Thus TNF α affects pathogenesis of psoriasis by activating T lymphocytes, enhancing T cell infiltration,²¹ and augmenting the proliferation of keratinocytes in psoriatic plaques.

TNF α in psoriatic synovium

Danning *et al* examined the immunostaining of a number of different cytokines in PsA synovium including TNF α , which was shown to localise both to the lining layer and to perivascular macrophages.³⁷ The distribution of TNF α expression in PsA is similar to that described in RA, although the extent of staining in PsA may be somewhat less as fewer macrophages infiltrate the synovial lining (fig 1). Using

quantitative polymerase chain reaction (PCR) we have also demonstrated increased proinflammatory cytokine mRNA expression including TNF α in the synovial tissue of 10 patients with PsA when compared with normal synovium.³⁸ Following methotrexate therapy, TNF α expression was reduced though not significantly. This indicates that at least some of the therapeutic benefit of methotrexate may be explained by downregulation of TNF α .

TNF α gene polymorphism analysis in psoriasis and PsA

A genetic predisposition to psoriasis and PsA has long been suspected. Early association studies in psoriasis focused attention on HLA-Cw6 in addition to HLA-B13, HLA-B17, and the class II antigen HLA-DR7. In PsA the main additional associations have been found to be with HLA-B27, chiefly in patients with predominant spinal disease, HLA-B38 and HLA-B39, and the class II antigen HLA-DR4. These findings suggest that the major histocompatibility complex (MHC) association with psoriasis lies close to the HLA-C region and the association with the articular manifestations lies in or close to the HLA-B region. Evidence would suggest that HLA-C itself is not the susceptibility gene for psoriasis but that there is a critical susceptibility region 170 kb in length centred 100 kb telomeric to HLA-C.³⁹⁻⁴¹

Other gene associations within the MHC region have been examined. Previous studies have suggested that TNF α promoter polymorphisms or a gene in linkage disequilibrium with TNF α predisposes the patient to, or increases susceptibility to, psoriasis and PsA. A more recent study determined whether functional cytokine gene polymorphisms influence disease susceptibility and phenotype in patients with PsA.⁴² Seven functional proinflammatory and anti-inflammatory polymorphisms were examined including TNF α -308 and TNF α +252. No significant difference was found in genotype frequency between the control and PsA patient populations. Of interest, the presence of joint erosions was significantly associated with both of these polymorphisms. Frequencies of these genotypes were also significantly different in the patients with PsA in whom the number of joint erosions in the hands and feet increased over a median two year follow up compared with a group of non-progressors. It was concluded that genotyping PsA patients early in their disease might help identify those with poor prognoses, who might then be selected for more aggressive treatment including TNF α inhibition.

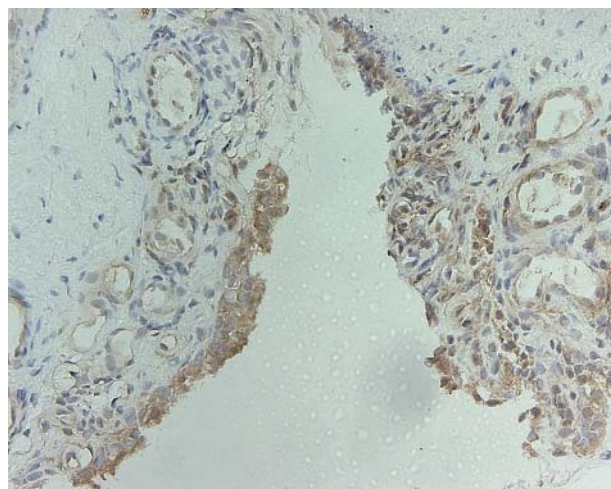


Figure 1 Immunohistochemical staining of tumour necrosis factor α protein in a section of psoriatic synovial membrane.

TNF α inhibition in psoriasis and PsA

Perhaps the most convincing evidence for an important role for TNF α in psoriasis and PsA comes from therapeutic studies of TNF α inhibition. Both etanercept, a fully human fusion protein consisting of two soluble TNF receptor domains linked to the FC portion of human IgG, and infliximab, a chimeric monoclonal IgG1 antibody, have been the subject of a number of clinical trials. Phase II and phase III clinical trials with etanercept have been completed in PsA, and a licence for use in PsA has been obtained. Impressive response rates were seen for both skin and joint outcome measures with 72% of patients treated with etanercept achieving a significant improvement in joint symptoms (PsA response criteria (PsARC)), as opposed to 31% of patients on placebo.^{43–44} Skin and joint responses are often seen within the first month of therapy, though the skin response may be slower and may not have reached its full level of improvement before six months. A more recent phase III study in 652 patients with psoriasis has confirmed the efficacy of etanercept with Psoriasis Area and Severity Index (PASI) scores improving by >75% in 44% of patients treated with 25 mg twice weekly and 59% of patients treated with 50 mg twice weekly (total number patients showing improvement = 205/652).⁴⁵ Studies with infliximab also suggest similar efficacy in both skin and joint manifestations, though to date no large scale phase III studies have been reported.^{46–48}

Although clinical trials have sometimes demonstrated a dramatic response to TNF α inhibition, only a few studies have examined the changes occurring in the skin or synovial tissue upon TNF α inhibition. Preliminary studies showed a decrease in cellular infiltration with normalisation of keratinocyte differentiation in the skin.⁴⁸ More recent studies have highlighted the vascular changes that occur in the skin upon TNF α inhibition²⁸; there is a reduction in vessel number, expression of VEGF, and expression of both angiopoietin-1 and angiopoietin-2. These studies show that the reduction in cellular infiltration may be secondary to a reduction in both angiogenesis and in cellular trafficking. Further studies of TNF α inhibition may help to identify genes associated with both good and poor response to treatment in addition to identifying novel genes downregulated by TNF α that may prove useful therapeutic targets.

ABNORMAL BONE REMODELLING IN PsA

Skeletal remodelling, a central process in bone growth, maintenance, and repair, is tightly regulated by a dynamic interplay between osteoclasts and osteoblasts.⁴⁹ Osteoclasts, derived from cells of monocytoid origin, resorb bone, and osteoblasts arise from mesenchymal lineage and produce bone matrix.⁵⁰ In pathological conditions, the fine balance between bone loss and production may be altered, resulting in excess bone resorption (osteolysis), new bone deposition, or both.⁵¹ Radiographs of PsA joints provide compelling evidence that bone remodelling is highly dysregulated in many patients. For example, *x* rays in PsA can manifest large eccentric erosions, marked joint space narrowing, and in the case of the arthritis mutilans subset, extensive tuft resorption and pencil in cup deformities.⁵² However, new bone formation, in the form of bulky syndesmophytes, bony ankylosis, and periostitis, is also a relatively common radiographic feature in PsA.

Until recently, the molecular events underlying osteoclast differentiation (osteoclastogenesis) and activation were not well understood. Elucidation of the receptor activator of nuclear factor κ B ligand (RANKL)–RANK signalling pathway, however, revealed the pivotal steps required for osteoclast formation and activation.⁵³ Specifically, RANKL, expressed on the surface of osteoblasts and stromal cells in the bone marrow and infiltrating T lymphocytes and

synoviocytes in the inflamed joint, binds to RANK, a cell associated TNF receptor related protein.⁵⁴ RANK is expressed on a variety of cell types including osteoclast precursors and osteoclasts. The interaction between RANKL and its receptor RANK, in the presence of macrophage colony stimulating factor (M-CSF), is necessary and sufficient for osteoclastogenesis and subsequent bone resorption. In addition, a decoy receptor for RANKL, osteoprotegerin, a molecule released by a wide array of cells, can bind to RANKL and neutralise bioactivity, thus inhibiting osteolysis.⁵⁵ Indeed, the ratio of RANKL to osteoprotegerin in a particular tissue is the primary factor determining the extent of osteolysis with a high ratio tipping the balance towards resorption.⁴⁹

Based on the hypothesis that the RANKL–RANK signalling pathway may be altered in the psoriatic joint, investigators analysed joint and bone tissues obtained from surgical samples.⁵⁶ They found abundant osteoclasts, in some cases with more than 30 nuclei, in deep resorption pits at the pannus–bone junction. Moreover, staining of adjacent inflamed PsA synovium with antibodies to RANKL revealed intense expression by the synovial lining cells, while osteoprotegerin staining was relatively faint and limited to the endothelium. Also, staining of tissues with anti-RANK antibodies showed a gradient of RANK+ cells (presumably osteoclast precursors) increasing in number from the blood vessels in the subsynovium to the pannus–bone junction where osteoclasts were prominently located. Bone from patients with osteoarthritis contained few osteoclasts and the synovial tissue did not express RANKL or osteoprotegerin.

In parallel studies, osteoclast precursors were found to be increased in the peripheral blood of PsA patients but not of healthy controls.⁵⁶ Furthermore, when PsA patients were treated with anti-TNF agents, the frequency of osteoclast precursors decreased significantly as early as two weeks after starting treatment with these agents. Thus, a model is emerging whereby elevated TNF, possibly triggered by events in the skin, leads to an increase in the frequency of circulating osteoclast precursors. Osteoclast precursors migrate to the psoriatic joint where they encounter relatively unopposed expression of RANKL, favouring differentiation and activation of osteoclasts. Once formed, osteoclasts are exposed to a variety of activating molecules in the PsA joint, including TNF and IL-1 that trigger osteoclast activation and osteolysis.⁵⁷

The molecular and cellular mechanisms responsible for the reciprocal process of pathological new bone formation in PsA need to be more carefully examined. Potential target molecules include VEGF, TGF β , and members of the bone morphogenic protein (BMP) family.⁵⁸ Certainly, additional studies that will likely involve suitable animal models are required to understand better the relationship between osteolysis and new bone formation in the psoriatic joint.

SUMMARY

The mechanisms of chronic inflammation in psoriatic skin and PsA joints appear to share many common immunopathological features. There are some shared genetic factors, which may also explain the role of TNF in this disease and the possible response to therapy in some patients. There is increasing evidence to support a role of T cells—CD4+, CD8+, and NK cells, as well as APCs. Early immune vascular changes are a prominent feature shared by skin and joints with apparent dysregulated angiogenesis linked to specific upregulation of growth factors. It is likely that cytokines, in particular TNF, and also TGF and many others, may be critically involved in driving the inflammatory process leading to production of MMPs and cartilage and bone degradation. The mechanisms of parallel new bone formation remain to be explained in this complex milieu.

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